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A FACILE AND GENERAL SYNTHESIS OF 4-HYDROXYCYCLOPENTENONES

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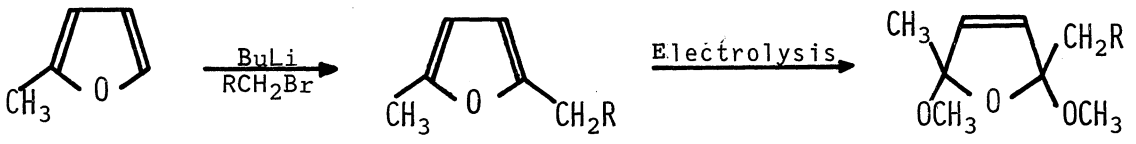
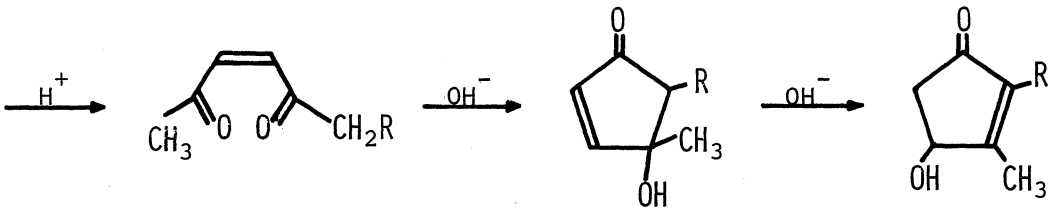
Various rethrolones were prepared in good yields simply from 2,5-disubstituted furans. The electrooxidation of 2,5-disubstituted dihydrofurans gave 2,5-dimethoxy-2,5-disubstituted dihydrofurans. Hydrolysis of electrooxidation products with ion enchange-resin, followed by the treatment with base gave rethrolones. Furthermore, this method was applicable for the synthesis of 2-alkyl-4-hydroxycyclopentenone.

We wish to report a remarkably simple synthetic method of 4-hydroxycyclopentenones, some of which have been known to be the essential component of some useful insecticides.[1] Furthermore, this method may indicate a wide potentiality in the syntheses of the related compounds of prostaglandins.



1 **2** **3**



cis-5 **6** **4**

2,5-Dimethoxydihydrofurans (**3**) were easily obtained by the anodic methoxylation[2] of the corresponding 2,5-disubstituted furans (**2**) prepared from 2-methylfuran (**1**) and alkyl bromide according to the method of Ramanthan.[3]

Compounds **3** were hydrolyzed at room temperature for an hour in the presence of acidic ion-exchange resin (Amberlite 120B). The resin was removed by filtration, and the treatment of the filtrate with 1% aqueous sodium carbonate at 100°C for two hours gave the 4-hydroxycyclopentenones (**4**)[4] as the exclusive products. Results are shown in Table I. All products were identified by the elemental and spectroscopic analyses and/or by the comparison with authentic samples.

Table I. Isolated Yield (%) and Boiling Point (°C/mmHg) of **2**, **3**, and **4**

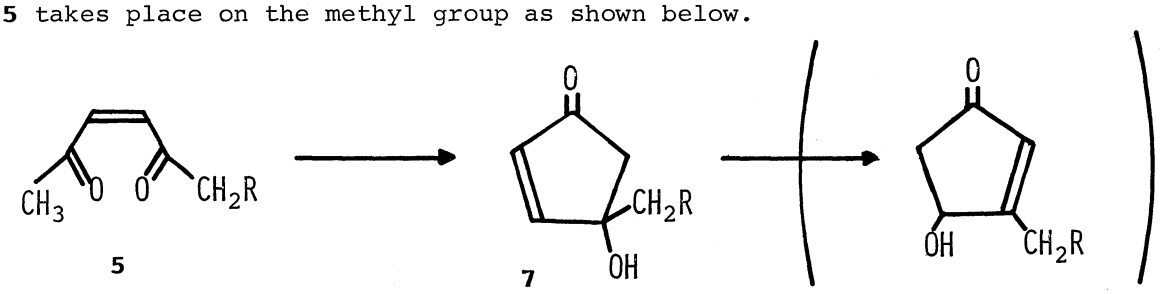
	R	Yield (%)			Boiling Point (°C/mmHg)		
		2	**3**	**4**[b,c]	**2**	**3**	**4**[b,c]
a	H	a	59	44		63/25	100-110/0.2
b	CH_2CH_3	78	78	55	135-138	58- 60/3	115-120/0.2
c	$CH_2CH_2CH_3$	84	71	59	155-157	70- 72/5	130-140/0.2
d	$CH_2CH{=}CH_3$	70	68	54	152-153	115-117/28	135-140/0.25
e	cis and trans[d] $CH_2CH{=}CHCH_3$	72	71	85	67- 69/11	122/15	110-115/0.15

a. Commercially available.
b. Isolated with column chromatography. **4**e was isolated with preparative thin-layer chromatography.
c. The isolated yields of the intermediates cis-**5**a[5] and cis-**5**e[6] are 98 and 96%, respectively.
d. Mixture.

In the course of the conversion of **3** to **4**, the intermediary formation of cis-diketone (cis-**5**) and hydroxycyclopentenone (**6**) was observed by VPC analysis, and furthermore, cis-**5**a and **6**a[7] (Yield, 67%) were isolated and transformed to the final product, **4**a. The yields were 43% from cis-**5**a and 75% from **6**a.

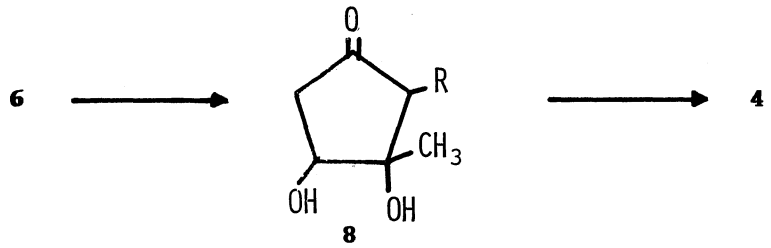
The acid-catalyzed hydrolysis of 2,5-dialkoxydihydrofuran (**3**) may yield both cis- and trans-1,4-diketone (cis-**5** and trans-**5**), though the ratio of the stereoisomers would depend on the nature of acid catalyst.[8] The treatment of **3**a (1.0g) with acidic ion-exchange resin (Amberlite 120B) (0.5g) in aqueous solution for 30 minutes gave only cis-**5**a (0.694g) which cyclized to **6**a (0.465g), while the cyclization of trans-**5**a generated by the hydrolysis of **3**a with dilute sulfuric acid did not take place. There would be two possible pathways in the cyclization of cis-**5** (R≠H). One of them is the formation of the compound of type **6** and the

compound of type **7** may be yielded by another route in which the proton abstraction from **5** takes place on the methyl group as shown below.



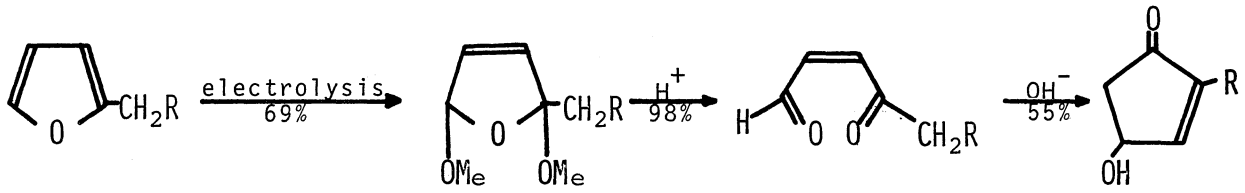
5 **7**

The cyclization of cis-**5** was, however, completely regiospecific and the formation of the compound of type **7** or the rearranged product of **7** was not detected. The isomerization of **6** to **4** may involve the intervention of diol (**8**),[9] though the formation of this compound was not observed in the present reaction.[10]



6 **8** **4**

Hydroxycyclopentenones of type **9** may be synthesized from mono substituted furans by this new method. For example, 2-propyl-4-hydroxycyclopentenone[11] was prepared from butylfuran in an overall yield of 37%.



R = Pr **10** **9**

In principle, there would be no particular restriction as to the structure of the group R in this reaction.[12] Thus, the combination of this new method with the reported reaction[13] would give a wide potentiality in the syntheses of the related compounds of prostaglandins. The study on the syntheses of some of the latter compounds is in progress.

References and Notes

(1) Representative synthetic reports for rethrolones;
(a) M. S. Schechter, N. Green, and F. B. Laforge, J. Am. Chem. Soc., 71, 3165 (1949);
(b) R. F. Romanet and R. H. Schlessinger, J. Am. Chem. Soc., 96, 3701 (1974), and references cited therein;
(c) R. A. Ellison, Synthesis, 1973, 397.

(2) Electrooxidation of furan (0.05mole) was accomplished in methanol (50cc) containing sodium methoxide (0.5g). The electrode was carbon rod. The electricity passed was 2.5F/mole. P. Nedenskov, N. Elming, J. T. Nielsen, and N. Clauson-Kass, Acta Chem. Scand., 9, 17 (1955).

(3) Methylfuran (0.2mole) was added at -25°C with stirring to a solution of buthyllithium (0.2mole) in THF (180cc) and stirring was continued for 4hr at -15°C. To this solution was added alkyl halide (0.2mole) diluted with THF (20cc). Stirring was continued over night at room temperature. V. Ramanthan and R. Levine, J. Org. Chem., 27, 1216 (1962).

(4) **4**a-e: ir; 1680cm^{-1}, nmr(δ_{TMS}ppm, in CCl_4); 2.15(s., 3H, methyl)

(5) cis-**5**a: nmr(δ_{TMS}ppm, in CCl_4); 2.18(s., 6H), 6.10(s., 2H).

(6) cis-**5**e: nmr(δ_{TMS}ppm, in CCl_4); 1.63(d., 3H), 2.30(s., 3H), 1.90-2.70(m., 4H), 5.35(m., 2H), 6.08(s., 2H).

(7) **6**a: nmr(δ_{TMS}ppm, in CCl_4); 1.46(s., 3H), 2.40(s., 2H) 5.96(d., 1H), 7.40(d., 1H).

(8) J. Levisalles, Bull. Soc. Chim. Fr., 1957, 997.

(9) Although the stereochemical requirement in a similar rearrangement of hydroxycyclopentenone was recently reported by Stork et al.,[13] the study on the mechanism of the rearrangement of **6** to **4** is currently in progress.

(10) The formation of a compound supposed to be an intermediate was observed with gas chromatographic analysis, though isolation of the sufficient amount of this compound for the analysis of structure was impossible.

(11) **9**: nmr(δ_{TMS}ppm, in CCl_4); 0.90(t., 3H). 1.50(m., 2H), 2.00-3.10(m., 4H), 4.92(m., 1H) 7.30(m., 1H).
10: nmr(δ_{TMS}ppm, in CCl_4); 0.89(t., 3H), 1.50(m., 4H), 2.55(t., 2H), 6.05(d. d., 1H), 6.81(d., 1H), 10.20(d., 1H).

(12) R group should not be hydroxyl group. T. Shono and Y. Matsumura, Tetrahedron Lett., 1976, 1363.

(13) G. Stork, C. Kowalski, and G. Garcia, J. Am. Chem. Soc., 97, 3258 (1975).

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